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# BIOASSAY OF PHOTODIELDRIN FOR POSSIBLE CARCINOGENICITY

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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# PHOTODIELDRIN

# FOR POSSIBLE CARCINOGENICITY

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CONTRIBUTORS: This report presents the results of the bioassay of photodieldrin for possible carcinogenicity, conducted for the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

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Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[6]. Statistical analyses were performed by Dr. J. R. Joiner[7], using methods selected for the bioassay program by Dr. J. J. Gart[8]. Chemicals used in this bioassay were analyzed under the direction of Dr. H. P. Burchfield, and the analytical results were reviewed by Dr. S. S. Olin[7].

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SUMMARY

A bioassay of dieldrin-free photodieldrin (synthesized by Gulf South Research Institute) for possible carcinogenicity was conducted by administering the test material in feed to Osborne-Mendel rats and B6C3F1 mice.

Groups of 50 rats of each sex were initially administered photodieldrin at one of two doses, either 5 or 10 ppm. Because of neurotoxic signs, doses in the females were reduced after 30 weeks. Total periods of treatment for low- and high-dose males and low-dose females were 80 weeks, followed by periods of 31 or 32 weeks of additional observation; the total period of treatment for the high-dose females was 59 weeks, followed by a period of additional observation of 53 weeks. The time-weighted average doses for the females were 3.4 or 7.5 ppm. Matched controls consisted of 10 untreated rats of each sex; pooled controls, used for statistical evaluation, consisted of the matched controls combined with 65 untreated male and 65 untreated female rats from similarly performed bioassays of six other test chemicals. All surviving rats were killed at 111-112 weeks.

Groups of 50 mice of each sex were administered photodieldrin at one of two doses, either 0.32 or 0.64 ppm, for 80 weeks, then observed for an additional 13 weeks. Matched controls consisted of groups of 10 untreated mice of each sex at each dose; pooled controls, used for statistical evaluation, consisted of the matched controls combined with 60 untreated male and 60 untreated female mice from similarly performed bioassays of six other test chemicals. All surviving mice were killed at 93 weeks.

Mean body weights attained by low- and high-dose male and female rats and mice were essentially unaffected by photodieldrin. Convulsions and hyperactivity were noted in treated male and female rats and in male mice. Mortality rates of either sex or either species were not affected by treatment.

In rats, benign tumors (adenoma and fibroadenoma) of the mammary gland in females showed a dose-related trend (P = 0.039) compared with matched, but not pooled, controls (8/72 pooled controls, 0/9 matched controls, 5/50 low-dose, 10/49 high-dose). Adenocarcinoma of the mammary gland occurred in two additional low-dose females. The incidences of these tumors in either of the treated groups were not significantly higher than those in the control groups using either matched or pooled controls. Three papillary and follicular-cell adenomas and one papillary adenocarcinoma of the thyroid occurred in the low-dose females, giving a statistically significant increase over the pooled controls (P = 0.022), but these thyroid tumors did not occur in the high-dose animals. The dose-related trend was not statistically significant using either pooled or matched controls, and the incidence in the low-dose group is not greater than that in the historical controls. In male rats, the incidence of hemangiomas showed a statistically significant dose-related trend (P = 0.021) using pooled controls, but the direct comparison of the three hemangiomas in the high-dose group with the pooled-control group was not statistically significant. Furthermore, three hemangiomas is a small number, and the tumors occurred in more than one anatomic site (two in the spleen, one in subcutaneous tissue). The occurrence of these tumors cannot clearly be associated with treatment.

In mice, there were no tumors that were statistically significant in treated groups of either sex.

It is concluded that under the conditions of this bioassay, photodieldrin was not carcinogenic for Osborne-Mendel rats or B6C3F1 mice.

## TABLE OF CONTENTS



## APPENDIXES

TABLES



FIGURES

# I. INTRODUCTION

Photodieldrin (CAS 13366-73-9; NCI C00599) is a photochemical conversion product of dieldrin with the systematic name 1,1,2,3,3a,7a-hexachloro-exo-5,6-epoxydecahydro-2,4,7-metheno-1H-cyclopenta[a] pentalene. It is a half-cage structure derived from the bridging of C-12 to C-9 in dieldrin with transfer of a C-12 hydrogen to C-10. Photoconversion is carried out in sunlight and by certain microorganisms that have been isolated from soil, water, rat intestine, and the rumen stomach contents of cows (Matsumura et al., 1970). The photochemical rearrangement and oxidation of aldrin and photoaldrin also will yield photodieldrin (Brooks, 1975). Under certain conditions, photodieldrin is persistent in the environment as a terminal residue of dieldrin (Matsumura, 1973; Brooks, 1975). Photodieldrin is more toxic than dieldrin to rats and mice but less toxic to dogs, chickens, and pheasants (Brooks, 1975).

Although it has never been produced commercially, photodieldrin was selected for testing in 1969 because it was a photochemical conversion product of dieldrin. At that time dieldrin was used extensively as a pesticide.

## II. MATERIALS AND METHODS

### A. Chemical

Gulf South Research Institute synthesized two batches of photodieldrin for use in the chronic study. The method, based on that described by Chau et al. (1971) for the preparation of photoheptachlor ketone, involved irradiating a solution of dieldrin in acetone at 2537 Å under nitrogen.

The first batch was synthesized from dieldrin obtained from Shell Chemical Company, Modesto, California, which had been purified by recrystallization. Photodieldrin was obtained in a 59% yield after three recrystallizations of the irradiated product from ethanol.

The second batch was prepared from technical-grade dieldrin, giving photodieldrin in a 48% yield after seven recrystallizations.

All analytical tests performed showed that both batches were identical to a reference sample of photodieldrin. Parameters compared included melting point (191.5-193°C), ir spectrum, thin-layer chromatograms, and gas-liquid chromatograms on two dissimilar columns. Neither batch contained any detectable residual dieldrin. The absence of dieldrin was also confirmed in

analyses of these batches by Shell Development Company, Modesto, California. No attempt was made to identify or quantitate impurities.

The chemical was stored in amber glass containers at 0°C.

B. Dietary Preparation

All diets were formulated using Wayne® Lab Blox (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of photodieldrin for each dietary concentration. The test chemical was first dissolved in a small amount of acetone (Mallinckrodt Inc., St. Louis, Mo.), which was then added to the feed. Corn oil (Louana®, Opelousas Refinery Co., Opelousas, La.) was also added to the feed, primarily as a dust suppressant, and the diets were mixed mechanically to assure homogeneity of the mixtures and evaporation of the acetone. Final diets, including those for the control groups of animals, contained corn oil equal to 2% of the final weight of feed. The diets were stored at approximately 17°C until used, but no longer than 1 week.

The stability of photodieldrin in feed was tested by determining the concentration of the chemical in formulated diets at intervals over a 7-day period. Diets containing 0.32, 0.64, 2.5, 5.0, or 10.0 ppm photodieldrin showed no change in concentration on standing at ambient temperature for this period.

As a quality control test on the accuracy of preparation of the diets, the concentration of photodieldrin was determined in different batches of formulated diets during the chronic study. The results are summarized in Appendix G. At each dietary concentration, the mean of the analytical concentrations for the checked samples was within 1.6% of the theoretical concentration, and the coefficient of variation was never more than 5.8%. Thus, the evidence indicates that the formulated diets were prepared accurately.

## C. Animals

Rats and mice of both sexes, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. The rats were of the Osborne-Mendel strain obtained from Battelle Memorial Institute, Columbus, Ohio, and the mice were B6C3F1 hybrids obtained from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. On arrival at the laboratory, all animals were quarantined for an acclimation period (rats for 9 days, mice for 14 days) and were then assigned to control and treated groups.

## D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature range was 22-24°C, and the relative

humidity was maintained at 40-70%. The air in each room was changed 10-12 times per hour. Fluorescent lighting provided illumination 10 hours per day. Food and water were supplied _ad libitum_.

The rats were housed individually in hanging galvanized steel mesh cages, and the mice were housed in plastic cages with filter bonnets, five per cage for females, and two or three per cage for males. Initially, rats were transferred once per week to clean cages; later in the study, cages were changed every 2 weeks. Mice were transferred once per week to clean cages covered with filter bonnets; bedding used for the mice was Absorb-Dri® (Lab Products, Inc., Garfield, N. J.). For rats, absorbent sheets under the cages were changed three times per week. Feeder jars and water bottles were changed and sterilized three times per week.

Cages for control and treated mice were placed on separate racks in the same room. Animal racks for both species were rotated laterally once per week; at the same time each cage was changed to a different position in the row within the same column. Rats receiving photodieldrin, along with their matched controls, were housed in a room by themselves. Mice receiving photodieldrin were maintained in a room housing mice administered aldrin (CAS

309-00-2) or captan (CAS 133-06-2), together with their respective matched controls.

## E. Subchronic Studies

Subchronic feeding studies were conducted with rats and mice to estimate the maximum tolerated doses of photodieldrin, on the basis of which low and high concentrations (hereinafter referred to as "low doses" and "high doses") were determined for administration in the chronic studies. In the subchronic studies, photodieldrin was added to the animal feed in twofold increasing concentrations, ranging from 2.5 to 80.0 ppm for rats and 0.01 to 0.32 ppm for mice. Control and treated groups each consisted of five male and five female animals. The chemical was provided in feed to treated groups for 6 weeks, followed by a 2-week period of observation. Because there were no deaths in the mice, and because the gains in body weights of the treated groups of mice were similar to those of the control group during the entire study, a second study was performed in mice, with doses ranging from 0.04 to 2.56 ppm. In the second study, the chemical was provided in feed to treated groups for 6 weeks, followed by a 3-week period of observation.

At 40 and 80 ppm, all rats died during week 2. In males receiving 20 ppm or less there was no evidence of significant

behavioral changes or other clinical signs except heavy shedding of hair. Throughout the 8-week study, all treated females lost weight. At 20 ppm the females appeared hyperactive. During week 6 tachypnea was noted in one female and hyperactivity in another female receiving 10 ppm photodieldrin. The low and high doses for rats were set at 5 and 10 ppm for the chronic studies.

There were no marked adverse effects in mice receiving 1.28 ppm. At 2.56 ppm all mice died by week 6. The low and high doses for mice were set at 0.32 and 0.64 ppm for the chronic studies.

## F. Designs of Chronic Studies

The designs of the chronic studies are shown in tables 1 and 2.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used for statistical comparisons. Matched controls from the current studies on photodieldrin were combined with matched controls from studies performed on malathion (CAS 121-75-5), tetrachlorvinphos (CAS 961-11-5), toxaphene (CAS 8001-35-2), lindane (CAS 58-89-9), endrin (CAS 72-20-8), and captan. The pooled controls for statistical tests using rats consisted of 75 males and 75 females; using mice, 80 males and 80 females. The studies on chemicals other than photodieldrin were also conducted at Gulf South Research Institute and overlapped the photodieldrin study

Table 1. Design of Photodieldrin Chronic Feeding Studies in Rats

| Sex and Treatment Group | Initial No. of Animals[a] | Photo-dieldrin in Diet (ppm) | Time on Study: Treated (weeks) | Time on Study: Untreated[b] (weeks) | Time-Weighted Average Dose[c] (ppm) |
|---|---|---|---|---|---|
| Male | | | | | |
| Matched-Control | 10 | 0 | | 111-112 | |
| Low-Dose | 50 | 5 | 80 | | 5 |
| | | 0 | | 31-32 | |
| High-Dose | 50 | 10 | 80 | | 10 |
| | | 0 | | 32 | |
| Female | | | | | |
| Matched-Control | 10 | 0 | | 111 | |
| Low-Dose | 50 | 5 | 30 | | |
| | | 2.5[d] | 50 | | 3.4 |
| | | 0 | | 32 | |
| High-Dose | 50 | 10 | 30 | | |
| | | 5[d] | 29 | | 7.5 |
| | | 0 | | 53 | |

[a]All animals were 35 days of age when placed on study.

[b]When diets containing photodieldrin were discontinued, high-dose females and their matched controls were fed control diets without corn oil for 8.5 weeks, then control diets (2% corn oil added) for an additional 44 weeks. All males, low-dose females, and their matched controls were fed control diets until termination of the study.

[c]Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm x no. of weeks at that dose})}{\Sigma(\text{no. of weeks receiving each dose})}$

[d]Because of neurotoxic signs, doses in female rats were reduced after 30 weeks.

Table 2. Design of Photodieldrin Chronic Feeding Studies in Mice

| Sex and Treatment Group | Initial No. of Animals[a] | Photodieldrin in Diet (ppm) | Time on Study: Treated (weeks) | Time on Study: Untreated[b] (weeks) |
|---|---|---|---|---|
| **Male** | | | | |
| Low-Dose Matched-Control | 10 | 0 | | 93 |
| High-Dose Matched-Control[c] | 10 | 0 | | 93 |
| Low-Dose | 50 | 0.32 | 80 | |
| | | 0 | | 13 |
| High-Dose[c] | 50 | | | |
| | | 0.64 | 80 | |
| | | 0 | | 13 |
| **Female** | | | | |
| Low-Dose Matched-Control | 10 | 0 | | 93 |
| High-Dose Matched-Control[c] | 10 | 0 | | 93 |
| Low-Dose | 50 | 0.32 | 80 | |
| | | 0 | | 13 |
| High-Dose[c] | 50 | 0.64 | 80 | 13 |
| | | 0 | | 13 |

[a]All animals were 35 days of age when placed on study.

[b]When diets containing photodieldrin were discontinued, mice received control diets until termination of the study.

[c]Due to high mortality caused by an error in the preparation of the feed mix, studies for high-dose male and high-dose female mice were terminated; the studies were then restarted using 10 additional matched-control mice.

by at least 1 year. The matched-control groups for the different test chemicals were of the same strain and from the same supplier, and they were examined by the same pathologists.

## G. Clinical and Pathologic Examinations

All animals were observed twice daily for signs of toxicity, weighed at regular intervals, and palpated for masses at each weighing. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The following tissues were examined microscopically: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, gallbladder (mice), pancreas, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary, and brain. Occasionally additional tissues were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few tissues from some animals were not examined, particularly from those animals that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

## H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit

procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a

significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the

first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated

from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as $p_t/p_c$ where $p_t$ is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and $p_c$ is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit

indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

# III. RESULTS - RATS

## A. Body Weights and Clinical Signs (Rats)

Mean body weights were generally comparable for treated and control rats of both sexes throughout the study (figure 1). During the first 16 weeks, the treated animals were generally comparable to the controls in appearance and behavior, with the exception of the high-dose females. Beginning in week 16, convulsions were observed in three high-dose females, and by week 24 convulsions were observed in a few animals in the high-dose male and low- and high-dose female groups. At week 28, all high-dose females appeared to be hyperactive. Concentrations of photodieldrin in feed were lowered for both high- and low-dose females at week 30.

During the second year of the study, various clinical signs including epistaxis, dermatitis, alopecia, rough hair coats, loss of weight, pale mucous membranes, tachypnea, hematuria, convulsions, hyperactivity, and abdominal distention were noted with increasing frequency in the treated groups.

## B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed photodieldrin in the diet

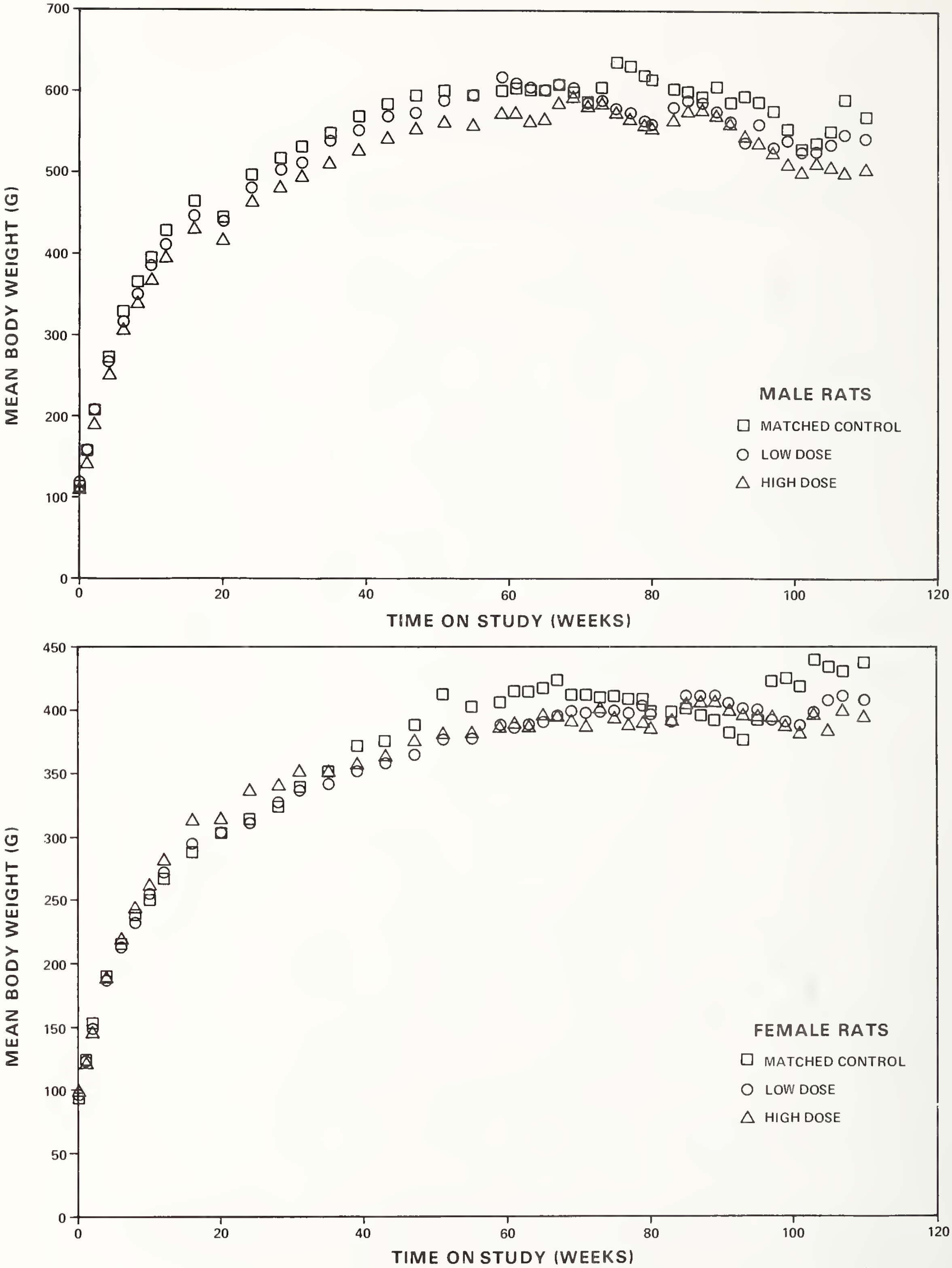



**Figure 1. Growth Curves for Rats Fed Photodieldrin in the Diet**

at the doses of this experiment, together with those of the controls, are shown in figure 2. The Tarone test results were not significant in either sex at the 0.05 level for positive dose-related trend in mortality over the period. In male rats, 46% of the high-dose group, 48% of the low-dose group, and 20% of the matched controls lived to the end of the study. Survival was longer in female rats than in the males. Sixty percent of the high-dose females, 62% of the low-dose females, and 70% of the matched controls lived to termination of the study. A sufficient number of animals were available for meaningful statistical analyses of the incidence of late-developing tumors.

## C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.

Neoplastic, degenerative, inflammatory, and proliferative lesions were encountered in both treated and control rats. The nonneoplastic lesions occurred infrequently or approximately as often among treated rats as among control rats.

Benign and malignant tumors of the pituitary gland occurred in 8/42 low-dose males and 7/46 high-dose males; benign tumors of the pituitary appeared in 5/48 low-dose females and 8/39 high-

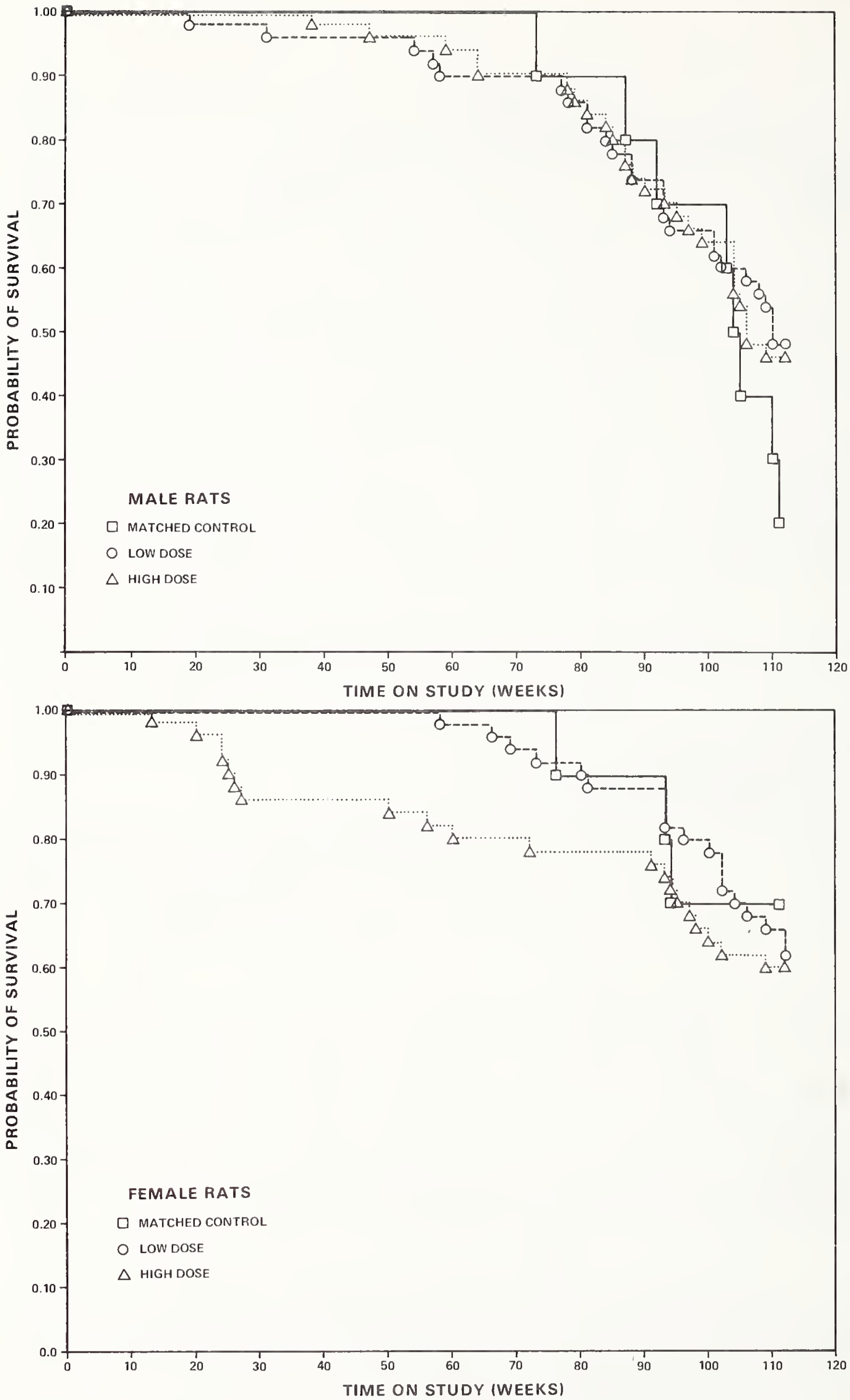



**Figure 2. Survival Curves for Rats Fed Photodieldrin in the Diet**

dose females. Benign and malignant tumors of the mammary gland occurred in 7/50 low-dose females and 10/49 high-dose females. These pituitary and mammary gland tumors were not found in rats of the matched-control groups. The remaining neoplastic lesions occurred with a random distribution and with a frequency in the treated rats similar to that in the controls.

With the exception of the tumors of the pituitary and mammary gland, the neoplastic lesions observed in rats occurred sporadically or with approximately equal frequency in treated animals and in controls. However, spontaneous tumors of the pituitary gland and mammary gland may occur at high incidences in the female Osborne-Mendel rat. Therefore, in the judgment of the pathologists, it is unlikely that photodieldrin was responsible for the induction of these tumors.

## D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

In female rats, when the incidences of papillary adenoma, papillary adenocarcinoma, and follicular-cell adenoma of the thyroid are grouped, the Fisher exact test shows that the incidence of

these combined tumors in the low-dose group is significantly higher than that in the pooled controls (P = 0.022). In male rats, follicular-cell adenoma was observed in one low-dose and one high-dose animal, and papillary adenocarcinoma was found in one high-dose animal. Experimental results for the combined group of papillary adenoma, papillary adenocarcinoma, and follicular-cell adenoma compiled to date from historical-control groups at this laboratory in the bioassay program indicate a spontaneous rate of less than 2% in females and 5% in males. These rates are not significantly different from those seen in the treated groups of this bioassay.

The combined incidence of adenoma and fibroadenoma of the mammary gland in female high-dose rats was double that in the low-dose animals (low-dose 5/50, high-dose 10/49), and no incidence was observed in the matched-control group; however, 8/72 (11%) were observed in the pooled-control group. The Cochran-Armitage test has a marginal significance using matched controls (P = 0.039), but this positive finding is not confirmed by the Fisher exact test results for either the low- or high-dose group or by the tests made using the pooled controls. The historical controls have an incidence of 42/235 (18%). Thus, the incidence in the matched-control group is lower than expected, and statistical significance may have occurred because of this low incidence

rather than the effect of the chemical. In male rats, no fibroadenoma or adenoma was observed. It is questionable whether tumors in the mammary glands of rats are associated with treatment.

Three hemangiomas were observed in the male high-dose group. The Cochran-Armitage test has a probability level of 0.021 when the pooled-control group is used, but this positive result is not supported by the Fisher exact test results, which show that the incidence in the high-dose group is not significant. When the Cochran-Armitage test result is based on the incidence in only one group, and this incidence has minimal significance, the trend analysis result is questionable. Two of the hemangiomas were observed in the spleen and one in subcutaneous tissue. Historical controls indicate a 0/240 incidence in male rats of this strain. There were no hemangiomas in the female rats.

Time-adjusted analyses, based on animals that lived beyond 52 weeks, performed on the incidence of chromophobe adenoma of the pituitary in male rats were not significant. When tumors are grouped for statistical analysis, as in adenoma and fibroadenoma of the mammary gland in female rats, the incidences of the individual components are not included in tables E1 and E2; however, a list of the incidences of each type of tumor is provided in Appendix A, tables A1 and A2.

# IV. RESULTS - MICE

## A. Body Weights and Clinical Signs (Mice)

Mean body weights were comparable for treated and control groups of both male and female mice throughout the study (figure 3). During the first year of the study, the treated animals were generally comparable to the controls in appearance and behavior. During this period, some loss of weight and a few cases of alopecia were noted. During the second year of the study, other clinical signs including discolored hair coats, alopecia, and abdominal distention were observed with an increasing frequency in treated groups. Hyperexcitability was noted in most of the treated males from weeks 65 and 66 to the end of the study.

## B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice fed photodieldrin in the diet at the doses of this experiment, together with those of the controls, are shown in figure 4. The separate control groups for the high-dose group and the low-dose group for each sex are combined and designated matched controls for survival analyses. In male mice, the Tarone test result for positive dose-related trend in mortality over the period is not significant. Ninety percent of the matched controls, 90% of the high-dose group, and

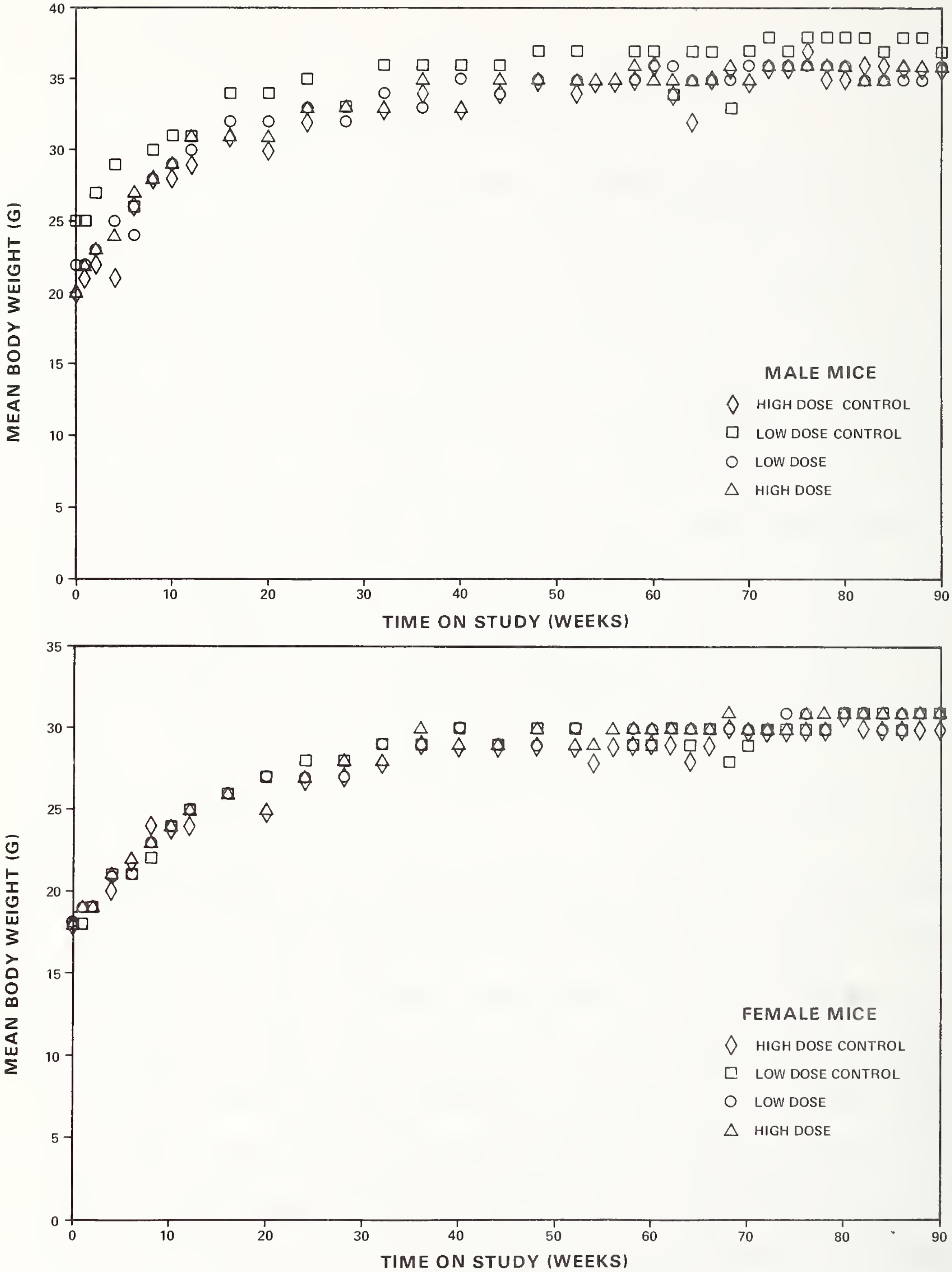
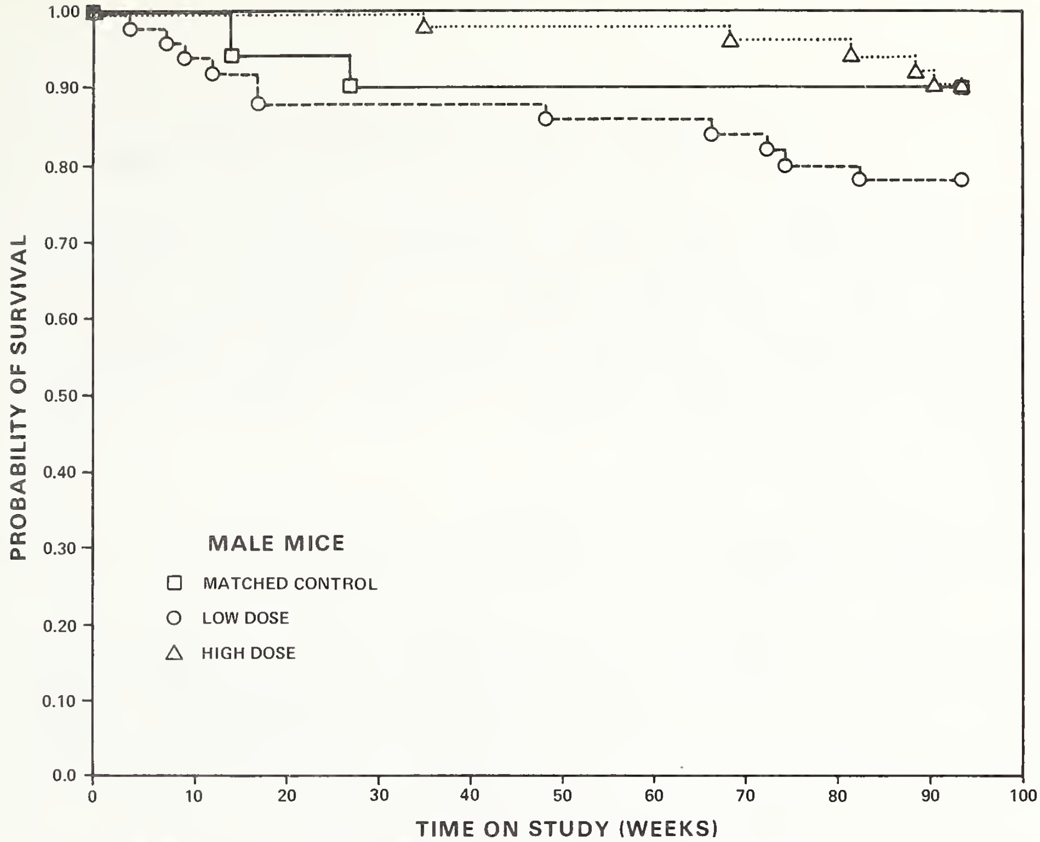



**Figure 3. Growth Curves for Mice Fed Photodieldrin in the Diet**



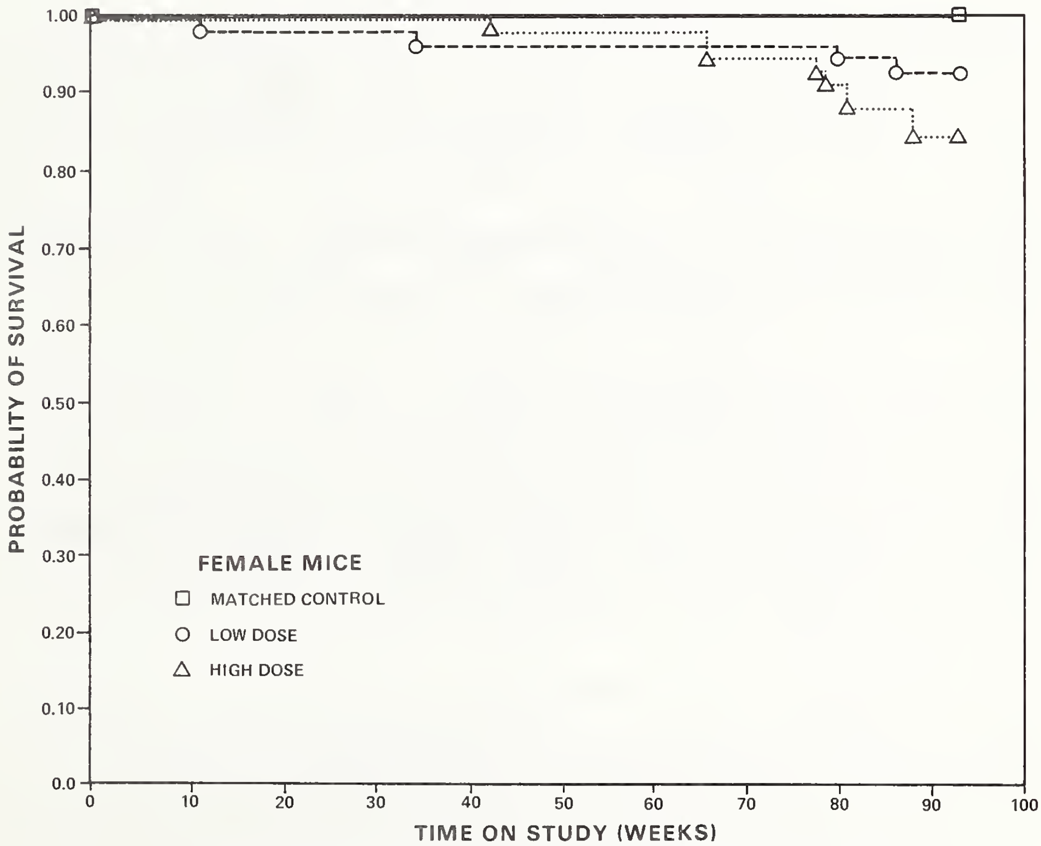




Figure 4. Survival Curves for Mice Fed Photodieldrin in the Diet

78% of the low-dose group lived to the end of the study. In females, the Tarone test has a probability level of 0.039, and over 80% of all the animals survived to termination of the study. A sufficient number of animals of both sexes were available for meaningful statistical analyses of the incidences of late-developing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

A variety of neoplasms occurred both in the control and treated groups. These neoplasms occurred with approximately equal frequency in treated and control mice or appeared in insignificant numbers. These lesions, however, are not uncommon in this strain of mouse independent of any treatment.

In addition to the neoplastic lesions, a number of degenerative, proliferative, and inflammatory changes were encountered also in animals of the treated and control groups. These nonneoplastic lesions are commonly seen in aged B6C3F1 mice.

In the judgment of the pathologists, there was no definitive evidence of the carcinogenicity of photodieldrin in mice.

## D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those specific primary tumors that were observed in at least 5% of one or more treated groups of either sex.

In neither sex does the incidence of any specific tumor show a statistically significant result. When the liver tumors in male mice are grouped for analysis (as in neoplastic nodules and hepatocellular carcinoma) the results are not significant. The incidence of neoplastic nodules, alone, is not included in table F1, since neither the low-dose nor the high-dose group has an incidence greater than 5%. A list of the incidences of each type of tumor is provided in Appendix B, tables B1 and B2.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included; this indicates the negative aspects of the results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by this chemical, which could not be detected under the conditions of this test.

# V. DISCUSSION

In this bioassay of photodieldrin, mean body weights were generally comparable for treated and control rats of both sexes and also for treated and control mice of both sexes. However, hyperexcitability and convulsions were observed in treated male and female rats and in male mice. This mode of toxicity, i.e., stimulation of the central and peripheral nervous system, is similar to that of the parent chemical, dieldrin, and other related organochlorine pesticides (Brooks, 1975). Although less than 50% of the treated male rats lived until termination of the study, survival among controls was also poor; mortality rates in either sex of either species were not affected by treatment.

In rats, benign tumors (adenoma and fibroadenoma) of the mammary gland in females showed a dose-related trend (P = 0.039) compared with matched controls, but not with pooled controls (pooled controls 8/72, matched controls 0/9, low-dose 5/50, high-dose 10/49). In addition, two other low-dose females had adenocarcinomas of the mammary gland. The incidences of these tumors in either of the treated groups were not significantly higher than those in the control groups using either matched or pooled controls, and thus, their occurrence cannot clearly be associated with treatment.

Three papillary and follicular-cell adenomas and one papillary adenocarcinoma of the thyroid occurred in the low-dose females, giving a statistically significant increase over the pooled controls (P = 0.022), but these thyroid tumors did not occur in the high-dose animals. The dose-related trend was not statistically significant using either pooled or matched controls, and the incidence in the low-dose group is not greater than that in the historical controls. Thus, these lesions are not considered to be related to treatment.

The incidence of hemangiomas in male rats showed a statistically significant dose-related trend (P = 0.021) using pooled controls, but the direct comparison of the three hemangiomas in the high-dose group with the pooled-control group was not statistically significant. In addition, three hemangiomas is a low number, and the tumors occurred in more than one anatomic site (two in the spleen, one in subcutaneous tissue). Thus, the hemangiomas in male rats are not considered to be related to treatment of the animals with photodieldrin.

In mice, there were no tumors that were statistically significant in treated groups of either sex.

In another bioassay, dieldrin was fed to mice at 2.5 and 5 ppm (NCI, 1977). In that study, hepatocellular carcinomas were

associated with treatment with dieldrin in male mice. The doses of dieldrin (2.5 and 5 ppm) were 7.8 times greater than the doses of photodieldrin, (0.32 and 0.64 ppm) used in the present study, which were not found to be associated with tumors of the liver in mice.

It is concluded that under the conditions of this bioassay, photodieldrin was not carcinogenic for Osborne-Mendel rats or B6C3F1 mice.

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS FED PHOTODIELDRIN IN THE DIET

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED PHOTODIELDRIN IN THE DIET

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 48 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 10 | 48 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (10) | (48) | (50) |
| SARCOMA, NOS | | 1 (2%) | 1 (2%) |
| HEMANGIOMA | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (10) | (48) | (49) |
| C-CELL CARCINOMA, METASTATIC | | 1 (2%) | |
| MIXED TUMOR, METASTATIC | | 1 (2%) | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (10) | (48) | (50) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (2%) | |
| LYMPHOCYTIC LEUKEMIA | | 1 (2%) | |
| #SPLEEN | (9) | (48) | (47) |
| FIBROSARCOMA | | 1 (2%) | |
| HEMANGIOMA | | | 2 (4%) |
| ANGIOMA | 1 (11%) | | |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (10) | (47) | (49) |
| NEOPLASTIC NODULE | | | 1 (2%) |
| #PANCREAS | (10) | (42) | (45) |
| SARCOMA, NOS, METASTATIC | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| URINARY SYSTEM | | | |
| #KIDNEY | (10) | (46) | (49) |
| MIXED TUMOR, MALIGNANT | | 2 (4%) | |
| † HAMARTOMA | 1 (10%) | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (5) | (42) | (46) |
| CARCINOMA,NOS | | 2 (5%) | 1 (2%) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| CHROMOPHOBE ADENOMA | | 6 (14%) | 5 (11%) |
| SARCOMA, NOS | | | 1 (2%) |
| #ADRENAL | (8) | (42) | (49) |
| CORTICAL CARCINOMA | | | 1 (2%) |
| PHEOCHROMOCYTOMA | | 1 (2%) | |
| #THYROID | (9) | (39) | (42) |
| PAPILLARY ADENOCARCINOMA | | | 1 (2%) |
| FOLLICULAR-CELL ADENOMA | | 1 (3%) | 1 (2%) |
| C-CELL ADENOMA | | 3 (8%) | 1 (2%) |
| C-CELL CARCINOMA | | 1 (3%) | |
| #PANCREATIC ISLETS | (10) | (42) | (45) |
| ISLET-CELL ADENOMA | 1 (10%) | | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (10) | (48) | (50) |
| PAPILLARY ADENOCARCINOMA | | | 1 (2%) |
| FIBROMA | | 1 (2%) | |
| #TESTIS | (10) | (46) | (49) |
| INTERSTITIAL-CELL TUMOR | 1 (10%) | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

† This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of lipocytes, tubular structures, and fibroblasts in varying proportions.

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | |
| *SKELETAL MUSCLE | (10) | (48) | (50) |
| SARCOMA, NOS | | 1 (2%) | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| *MULTIPLE ORGANS | (10) | (48) | (50) |
| FIBROUS HISTIOCYTOMA, MALIGNANT | | 1 (2%) | |
| LEIOMYOSARCOMA | | 1 (2%) | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| NATURAL DEATH@ | 2 | 13 | 11 |
| MORIBUND SACRIFICE | 6 | 13 | 16 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 2 | 24 | 23 |
| ANIMAL MISSING | | | |

@ INCLUDES AUTOLYZED ANIMALS

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 4 | 20 | 15 |
| TOTAL PRIMARY TUMORS | 4 | 25 | 18 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 4 | 11 | 10 |
| TOTAL BENIGN TUMORS | 4 | 13 | 10 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | | 11 | 7 |
| TOTAL MALIGNANT TUMORS | | 12 | 7 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | 2 | 1 |
| TOTAL SECONDARY TUMORS | | 2 | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT | | | 1 |
| TOTAL UNCERTAIN TUMORS | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

## TABLE A2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED PHOTODIELDRIN IN THE DIET

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 9 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 9 | 50 | 48 |
| **INTEGUMENTARY SYSTEM** | | | |
| NONE | | | |
| **RESPIRATORY SYSTEM** | | | |
| NONE | | | |
| **HEMATOPOIETIC SYSTEM** | | | |
| *MULTIPLE ORGANS | (9) | (50) | (49) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | 1 (2%) |
| **CIRCULATORY SYSTEM** | | | |
| #HEART/VENTRICLE | (9) | (49) | (47) |
| FIBROMA | 1 (11%) | | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (9) | (49) | (46) |
| HEPATOCELLULAR CARCINOMA | | 1 (2%) | |
| #STOMACH | (9) | (46) | (46) |
| LEIOMYOMA | | 1 (2%) | |
| **URINARY SYSTEM** | | | |
| #KIDNEY | (9) | (49) | (48) |
| CARCINOMA,NOS | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (8) | (48) | (39) |
| ADENOMA, NOS | | 1 (2%) | |
| CHROMOPHOBE ADENOMA | | 4 (8%) | 8 (21%) |
| #ADRENAL | (9) | (48) | (43) |
| CORTICAL ADENOMA | | 1 (2%) | |
| #THYROID | (9) | (43) | (39) |
| PAPILLARY ADENOMA | | 2 (5%) | |
| PAPILLARY ADENOCARCINOMA | | 1 (2%) | |
| FOLLICULAR-CELL ADENOMA | | 1 (2%) | |
| C-CELL ADENOMA | | 2 (5%) | 1 (3%) |
| C-CELL CARCINOMA | | | 1 (3%) |
| #PANCREATIC ISLETS | (9) | (49) | (42) |
| ISLET-CELL ADENOMA | | | 2 (5%) |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (9) | (50) | (49) |
| ADENOMA, NOS | | | 1 (2%) |
| ADENOCARCINOMA, NOS | | 2 (4%) | |
| FIBROMA | | | 1 (2%) |
| FIBROADENOMA | | 5 (10%) | 9 (18%) |
| #UTERUS | (6) | (42) | (37) |
| ENDOMETRIAL STROMAL POLYP | 1 (17%) | 5 (12%) | 6 (16%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| NATURAL DEATH@ | 3 | 3 | 8 |
| MORIBUND SACRIFICE | | 16 | 12 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 7 | 31 | 30 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 2 | 20 | 26 |
| TOTAL PRIMARY TUMORS | 2 | 26 | 31 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 2 | 18 | 24 |
| TOTAL BENIGN TUMORS | 2 | 22 | 28 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | | 4 | 3 |
| TOTAL MALIGNANT TUMORS | | 4 | 3 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | |
| TOTAL SECONDARY TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

MICE FED PHOTODIELDRIN IN THE DIET

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED PHOTODIELDRIN IN THE DIET

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 10 | 47 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 8 | 10 | 47 | 49 |
| INTEGUMENTARY SYSTEM | | | | |
| NONE | | | | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (10) | (10) | (47) | (49) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | 1 (2%) | 4 (8%) |
| HEMATOPOIETIC SYSTEM | | | | |
| *MULTIPLE ORGANS | (10) | (10) | (47) | (49) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (10) | (9) | (47) | (47) |
| NEOPLASTIC NODULE | | | | 1 (2%) |
| HEPATOCELLULAR CARCINOMA | 3 (30%) | | 10 (21%) | 9 (19%) |
| HEMANGIOMA | | | 1 (2%) | |
| URINARY SYSTEM | | | | |
| NONE | | | | |
| ENDOCRINE SYSTEM | | | | |
| NONE | | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | | |
| #TESTIS | (9) | (10) | (46) | (47) |
| HEMANGIOMA | | | 1 (2%) | |
| NERVOUS SYSTEM | | | | |
| NONE | | | | |
| SPECIAL SENSE ORGANS | | | | |
| *EYE/LACRIMAL GLAND | *(10) | (10) | (47) | (49) |
| PAPILLARY CYSTADENOMA, NOS | | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| NONE | | | | |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| NATURAL DEATH@ | 2 | | 6 | 1 |
| MORIBUND SACRIFICE | | | 5 | 4 |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | |
| TERMINAL SACRIFICE | 8 | 10 | 39 | 45 |
| ANIMAL MISSING | | | | |

@ INCLUDES AUTOLYZED ANIMALS

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 3 | | 14 | 13 |
| TOTAL PRIMARY TUMORS | 3 | | 14 | 15 |
| TOTAL ANIMALS WITH BENIGN TUMORS | | | 3 | 5 |
| TOTAL BENIGN TUMORS | | | 3 | 5 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 3 | | 11 | 9 |
| TOTAL MALIGNANT TUMORS | 3 | | 11 | 9 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | | |
| TOTAL SECONDARY TUMORS | | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | | 1 |
| TOTAL UNCERTAIN TUMORS | | | | 1 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

# TABLE B2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED PHOTODIELDRIN IN THE DIET

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 10 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 10 | 10 | 49 | 49 |
| INTEGUMENTARY SYSTEM | | | | |
| *SUBCUT TISSUE | (10) | (10) | (49) | (49) |
| HEMANGIOMA | | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (10) | (10) | (48) | (48) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (10%) | | | 2 (4%) |
| HEMATOPOIETIC SYSTEM | | | | |
| *MULTIPLE ORGANS | (10) | (10) | (49) | (49) |
| MALIGNANT LYMPHOMA, NOS | | 1 (10%) | | 1 (2%) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | 1 (10%) | 1 (2%) | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | 3 (6%) |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (9) | (10) | (43) | (47) |
| HEPATOCELLULAR CARCINOMA | | | | 1 (2%) |
| URINARY SYSTEM | | | | |
| NONE | | | | |
| ENDOCRINE SYSTEM | | | | |
| NONE | | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | | |
| *MAMMARY GLAND | (10) | (10) | (49) | (49) |
| HAMARTOMA | | | 1 (2%) | |
| #OVARY | (9) | (8) | (45) | (46) |
| CYSTADENOMA, NOS | | | | 1 (2%) |
| NERVOUS SYSTEM | | | | |
| NONE | | | | |
| SPECIAL SENSE ORGANS | | | | |
| NONE | | | | |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| NONE | | | | |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| ANIMAL DISPOSITION SUMMARY | | | | |
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| NATURAL DEATH@ | | | 3 | 3 |
| MORIBUND SACRIFICE | | | 1 | 5 |
| SCHEDULED SACRIFICE | | | | |
| ACCIDENTALLY KILLED | | | | |
| TERMINAL SACRIFICE | 10 | 10 | 46 | 42 |
| ANIMAL MISSING | | | | |

@ INCLUDES AUTOLYZED ANIMALS

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| TUMOR SUMMARY | | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 1 | 2 | 3 | 8 |
| TOTAL PRIMARY TUMORS | 1 | 2 | 3 | 8 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 1 | | 2 | 3 |
| TOTAL BENIGN TUMORS | 1 | | 2 | 3 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | | 2 | 1 | 5 |
| TOTAL MALIGNANT TUMORS | | 2 | 1 | 5 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | | |
| TOTAL SECONDARY TUMORS | | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC | | | | |
| TOTAL UNCERTAIN TUMORS | | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN RATS FED PHOTODIELDRIN IN THE DIET

## TABLE C1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED PHOTODIELDRIN IN THE DIET

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 48 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 10 | 48 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (10) | (48) | (50) |
| ULCER, NOS | | 1 (2%) | |
| INFLAMMATION, FOCAL GRANULOMATOU | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (10) | (48) | (49) |
| EMPHYSEMA, NOS | | 2 (4%) | |
| ATELECTASIS | | 1 (2%) | |
| PNEUMONIA, CHRONIC MURINE | | 1 (2%) | |
| #LUNG/ALVEOLI | (10) | (48) | (49) |
| EMPHYSEMA, NOS | | 3 (6%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #SPLEEN | (9) | (48) | (47) |
| CONGESTION, NOS | | | 1 (2%) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| FIBROSIS, FOCAL | | 1 (2%) | |
| HEMOSIDEROSIS | | | 1 (2%) |
| CIRCULATORY SYSTEM | | | |
| #HEART | (10) | (47) | (48) |
| DEGENERATION PARENCHYMATOUS | | | 1 (2%) |
| DEGENERATION, HYDROPIC | | | 1 (2%) |
| #HEART/ATRIUM | (10) | (47) | (48) |
| THROMBOSIS, NOS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ENDOCARDIUM | (10) | (47) | (48) |
| FIBROSIS, FOCAL | | 1 (2%) | |
| *AORTA | (10) | (48) | (50) |
| THROMBOSIS, NOS | | | 1 (2%) |
| SCLEROSIS | | | 1 (2%) |
| MEDIAL CALCIFICATION | | | 1 (2%) |
| CALCIFICATION, NOS | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (10) | (47) | (49) |
| DEGENERATION PARENCHYMATOUS | 1 (10%) | 3 (6%) | 2 (4%) |
| METAMORPHOSIS FATTY | 1 (10%) | 5 (11%) | 9 (18%) |
| CYTOLOGIC DEGENERATION | | 1 (2%) | |
| ANGIECTASIS | 1 (10%) | 3 (6%) | 5 (10%) |
| *BILE DUCT | (10) | (48) | (50) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| #PANCREAS | (10) | (42) | (45) |
| PERIARTERITIS | | | 1 (2%) |
| NECROSIS, FAT | | 1 (2%) | |
| #STOMACH | (10) | (45) | (46) |
| ULCER, NOS | | 1 (2%) | |
| CALCIFICATION, DYSTROPHIC | 3 (30%) | | |
| #GASTRIC MUCOSA | (10) | (45) | (46) |
| EROSION | | | 1 (2%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (10) | (46) | (49) |
| HYDRONEPHROSIS | | 1 (2%) | |
| GLOMERULONEPHRITIS, NOS | 3 (30%) | 4 (9%) | 6 (12%) |
| INFLAMMATION, CHRONIC | 2 (20%) | 15 (33%) | 13 (27%) |
| INFLAMMATION, CHRONIC DIFFUSE | | | 1 (2%) |
| #KIDNEY/PELVIS | (10) | (46) | (49) |
| INFLAMMATION, NOS | | | 1 (2%) |
| #URINARY BLADDER | (10) | (43) | (45) |
| INFLAMMATION, ACUTE NECROTIZING | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, EPITHELIAL | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (5) | (42) | (46) |
| CYST, NOS | | 1 (2%) | 1 (2%) |
| MULTIPLE CYSTS | | 1 (2%) | |
| CONGESTION, NOS | | 1 (2%) | |
| HYPERPLASIA, NOS | | 3 (7%) | |
| HYPERPLASIA, CHROMOPHOBE-CELL | | | 1 (2%) |
| ANGIECTASIS | 1 (20%) | | 1 (2%) |
| #ADRENAL | (8) | (42) | (49) |
| NECROSIS, HEMORRHAGIC | | 1 (2%) | |
| ANGIECTASIS | | | 1 (2%) |
| #ADRENAL CORTEX | (8) | (42) | (49) |
| CYST, NOS | | 1 (2%) | |
| METAMORPHOSIS FATTY | | 1 (2%) | |
| HYPERPLASIA, DIFFUSE | | | 1 (2%) |
| #THYROID | (9) | (39) | (42) |
| FOLLICULAR CYST, NOS | | | 2 (5%) |
| HYPERPLASIA, FOLLICULAR-CELL | 1 (11%) | 5 (13%) | 2 (5%) |
| #PARATHYROID | (6) | (15) | (25) |
| HYPERPLASIA, NOS | 1 (17%) | | |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (10) | (48) | (50) |
| NECROSIS, FAT | | 1 (2%) | |
| *MAMMARY LOBULE | (10) | (48) | (50) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #PROSTATE | (10) | (40) | (46) |
| INFLAMMATION, NOS | 1 (10%) | 1 (3%) | |
| INFLAMMATION, SUPPURATIVE | 1 (10%) | | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, ACUTE SUPPURATIVE | | | 1 (2%) |
| HYPERPLASIA, NOS | 1 (10%) | | |
| *SEMINAL VESICLE | (10) | (48) | (50) |
| DEGENERATION, CYSTIC | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #TESTIS | (10) | (46) | (49) |
| ATROPHY, NOS | 3 (30%) | 9 (20%) | 12 (24%) |
| ATROPHY, FOCAL | | 1 (2%) | |
| HYPERPLASIA, INTERSTITIAL CELL | | 1 (2%) | |
| **NERVOUS SYSTEM** | | | |
| NONE | | | |
| **SPECIAL SENSE ORGANS** | | | |
| NONE | | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| NONE | | | |
| **BODY CAVITIES** | | | |
| *MESENTERY | (10) | (48) | (50) |
| THROMBOSIS, NOS | 1 (10%) | | |
| PERIARTERITIS | 1 (10%) | | 3 (6%) |
| **ALL OTHER SYSTEMS** | | | |
| NONE | | | |
| **SPECIAL MORPHOLOGY SUMMARY** | | | |
| NO LESION REPORTED | 1 | 8 | 8 |
| AUTO/NECROPSY/NO HISTO | | | 1 |
| AUTOLYSIS/NO NECROPSY | | 2 | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

# TABLE C2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED PHOTODIELDRIN IN THE DIET

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 9 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 9 | 50 | 48 |
| **INTEGUMENTARY SYSTEM** | | | |
| NONE | | | |
| **RESPIRATORY SYSTEM** | | | |
| #LUNG/BRONCHIOLE | (9) | (50) | (47) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #LUNG | (9) | (50) | (47) |
| CONGESTION, NOS | | | 2 (4%) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, FOCAL | | 2 (4%) | |
| #LUNG/ALVEOLI | (9) | (50) | (47) |
| EMPHYSEMA, NOS | | 1 (2%) | 1 (2%) |
| **HEMATOPOIETIC SYSTEM** | | | |
| #SPLEEN | (9) | (49) | (46) |
| CONGESTION, NOS | | 1 (2%) | |
| HYPOPLASIA, LYMPHOID | | 1 (2%) | |
| **CIRCULATORY SYSTEM** | | | |
| NONE | | | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (9) | (49) | (46) |
| HEMORRHAGE | | 1 (2%) | |
| LYMPHOCYTIC INFILTRATE | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DEGENERATION PARENCHYMATOUS | | 2 (4%) | |
| NECROSIS, NOS | | 1 (2%) | |
| NECROSIS, FOCAL | 1 (11%) | | |
| METAMORPHOSIS FATTY | | 3 (6%) | |
| ANGIECTASIS | 1 (11%) | 2 (4%) | 8 (17%) |
| #HEPATIC CAPSULE | (9) | (49) | (46) |
| HEMORRHAGE | | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (9) | (49) | (46) |
| METAMORPHOSIS FATTY | | | 1 (2%) |
| *BILE DUCT | (9) | (50) | (49) |
| HYPERPLASIA, NOS | | 2 (4%) | |
| #PANCREAS | (9) | (49) | (42) |
| METAMORPHOSIS FATTY | | 1 (2%) | |
| #GASTRIC MUCOSA | (9) | (46) | (46) |
| NECROSIS, FOCAL | | 1 (2%) | |
| #GASTRIC FUNDUS | (9) | (46) | (46) |
| ABRADED WOUND | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (9) | (49) | (48) |
| CYST, NOS | | | 1 (2%) |
| GLOMERULONEPHRITIS, NOS | | | 4 (8%) |
| INFLAMMATION, NOS | | 1 (2%) | |
| INFLAMMATION, FOCAL | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | 1 (11%) | | |
| #KIDNEY/CORTEX | (9) | (49) | (48) |
| MULTILOCULAR CYST | | 1 (2%) | |
| #KIDNEY/PELVIS | (9) | (49) | (48) |
| HYPERPLASIA, EPITHELIAL | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (8) | (48) | (39) |
| CONGESTION, NOS | 2 (25%) | | 1 (3%) |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HEMORRHAGE | 2 (25%) | 2 (4%) | 2 (5%) |
| DEGENERATION, CYSTIC | | | 1 (3%) |
| ANGIECTASIS | 1 (13%) | 5 (10%) | 3 (8%) |
| #ADRENAL | (9) | (48) | (43) |
| CYST, NOS | | 1 (2%) | |
| HEMORRHAGE | | 2 (4%) | 2 (5%) |
| DEGENERATION, NOS | | | 1 (2%) |
| DEGENERATION, CYSTIC | | 1 (2%) | |
| NECROSIS, FOCAL | | 1 (2%) | |
| NECROSIS, HEMORRHAGIC | | | 1 (2%) |
| METAMORPHOSIS FATTY | | 1 (2%) | 1 (2%) |
| ANGIECTASIS | | 2 (4%) | 4 (9%) |
| #ADRENAL CORTEX | (9) | (48) | (43) |
| DEGENERATION, NOS | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | 1 (2%) | |
| METAMORPHOSIS FATTY | 1 (11%) | | |
| ANGIECTASIS | | 2 (4%) | |
| #THYROID | (9) | (43) | (39) |
| HYPERPLASIA, C-CELL | | 1 (2%) | |
| #PANCREATIC ISLETS | (9) | (49) | (42) |
| HYPERPLASIA, NOS | 1 (11%) | | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY LOBULE | (9) | (50) | (49) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| #UTERUS | (6) | (42) | (37) |
| METAPLASIA, SQUAMOUS | | 1 (2%) | |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | 3 | 12 | 13 |
| AUTO/NECROPSY/NO HISTO | | | 1 |
| AUTOLYSIS/NO NECROPSY | 1 | | 1 |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN MICE FED PHOTODIELDRIN IN THE DIET

## TABLE D1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED PHOTODIELDRIN IN THE DIET

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 10 | 47 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 8 | 10 | 47 | 49 |
| INTEGUMENTARY SYSTEM | | | | |
| NONE | | | | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG | (10) | (10) | (47) | (49) |
| HEMORRHAGE | | 1 (10%) | | |
| INFLAMMATION, FOCAL | | | 1 (2%) | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 1 (10%) | | |
| HEMATOPOIETIC SYSTEM | | | | |
| #LYMPH NODE | (8) | (9) | (42) | (44) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| #MESENTERIC L. NODE | (8) | (9) | (42) | (44) |
| INFLAMMATION, NOS | | | | 1 (2%) |
| #SUBSCAPULAR LYMPH NO | (8) | (9) | (42) | (44) |
| INFARCT, NOS | | | | 1 (2%) |
| #THYMUS | | (1) | | |
| HYPERPLASIA, LYMPHOID | | 1 (100%) | | |
| CIRCULATORY SYSTEM | | | | |
| NONE | | | | |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (10) | (9) | (47) | (47) |
| INFARCT, NOS | | | | 2 (4%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| HYPERPLASIA, NODULAR | | 3 (33%) | | 3 (6%) |
| URINARY SYSTEM | | | | |
| NONE | | | | |
| ENDOCRINE SYSTEM | | | | |
| NONE | | | | |
| REPRODUCTIVE SYSTEM | | | | |
| NONE | | | | |
| NERVOUS SYSTEM | | | | |
| #BRAIN | (9) | (10) | (45) | (49) |
| CORPORA AMYLACEA | 1 (11%) | 1 (10%) | | 3 (6%) |
| SPECIAL SENSE ORGANS | | | | |
| NONE | | | | |
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| NONE | | | | |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | 4 | 6 | 32 | 30 |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| AUTO/NECROPSY/NO HISTO | 2 | | | |
| AUTOLYSIS/NO NECROPSY | | | 3 | 1 |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE FED PHOTODIELDRIN IN THE DIET

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 10 | 10 | 50 | 50 |
| ANIMALS NECROPSIED | 10 | 10 | 49 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 10 | 10 | 49 | 49 |
| INTEGUMENTARY SYSTEM | | | | |
| NONE | | | | |
| RESPIRATORY SYSTEM | | | | |
| #LUNG/BRONCHIOLE | (10) | (10) | (48) | (48) |
| HYPERPLASIA, LYMPHOID | | | | 1 (2%) |
| #LUNG | (10) | (10) | (48) | (48) |
| PNEUMONIA, ASPIRATION | | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | | |
| #SPLEEN | (10) | (10) | (48) | (48) |
| HYPERPLASIA, LYMPHOID | | 1 (10%) | 2 (4%) | 3 (6%) |
| CIRCULATORY SYSTEM | | | | |
| #MYOCARDIUM | (10) | (10) | (48) | (48) |
| FIBROSIS, FOCAL | | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | | |
| #LIVER | (9) | (10) | (43) | (47) |
| DEGENERATION PARENCHYMATOUS | | | | 3 (6%) |
| METAMORPHOSIS FATTY | | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, NODULAR | | 1 (10%) | 3 (7%) | 1 (2%) |
| HYPERPLASIA, DIFFUSE | 1 (11%) | | 2 (5%) | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) | |
| NODULAR REGENERATION | | | 1 (2%) | |
| #PANCREAS | (10) | (10) | (47) | (46) |
| ATROPHY, NOS | | | 1 (2%) | |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| URINARY SYSTEM | | | | |
| #KIDNEY | (10) | (10) | (48) | (48) |
| INFLAMMATION, INTERSTITIAL | | 1 (10%) | | |
| #KIDNEY/CORTEX | (10) | (10) | (48) | (48) |
| HYPERPLASIA, LYMPHOID | | | | 1 (2%) |
| #URINARY BLADDER | (7) | (10) | (41) | (42) |
| HYPERPLASIA, LYMPHOID | | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | | |
| NONE | | | | |
| REPRODUCTIVE SYSTEM | | | | |
| #UTERUS/ENDOMETRIUM | (10) | (9) | (45) | (43) |
| INFLAMMATION, SUPPURATIVE | | | | 1 (2%) |
| DEGENERATION, CYSTIC | | | | 3 (7%) |
| HYPERPLASIA, CYSTIC | 2 (20%) | 2 (22%) | 7 (16%) | 6 (14%) |
| #OVARY/OVIDUCT | (10) | (9) | (45) | (43) |
| INFLAMMATION, NOS | | | 1 (2%) | |
| #OVARY | (9) | (8) | (45) | (46) |
| FOLLICULAR CYST, NOS | 1 (11%) | | | |
| POLYCYSTIC OVARY | | | | 1 (2%) |
| HEMORRHAGE | | | | 1 (2%) |
| INFLAMMATION, NOS | | 4 (50%) | | 1 (2%) |
| INFLAMMATION, SUPPURATIVE | 1 (11%) | | 8 (18%) | 2 (4%) |
| INFLAMMATION, ACUTE | | | 1 (2%) | |
| INFLAMMATION, ACUTE SUPPURATIVE | | | 4 (9%) | |
| ABSCESS, NOS | 1 (11%) | | | |
| INFLAMMATION ACUTE AND CHRONIC | | | 1 (2%) | |
| NERVOUS SYSTEM | | | | |
| #BRAIN | (10) | (10) | (47) | (49) |
| CORPORA AMYLACEA | | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | | |
| NONE | | | | |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | LOW DOSE CONTROL | HIGH DOSE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | | |
| NONE | | | | |
| BODY CAVITIES | | | | |
| *PERITONEAL CAVITY | (10) | (10) | (49) | (49) |
| INFLAMMATION, CHRONIC | | | | 1 (2%) |
| ALL OTHER SYSTEMS | | | | |
| NONE | | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | | |
| NO LESION REPORTED | 4 | 1 | 23 | 24 |
| AUTOLYSIS/NO NECROPSY | | | 1 | 1 |

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS

IN RATS FED PHOTODIELDRIN IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Photodieldrin in the Diet[a]

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Pituitary: Carcinoma, NOS[b] | 1/62 (2) | 0/5 (0) | 2/42 (5) | 1/46 (2) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 2.952 | 1.348 |
| Lower Limit | | | 0.158 | 0.017 |
| Upper Limit | | | 169.961 | 103.525 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.045 | 0.010 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 93 | 106 |
| Pituitary: Carcinoma, NOS or Adenocarcinoma, NOS[b] | 1/62 (2) | 0/5 (0) | 2/42 (5) | 2/46 (4) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 2.952 | 2.696 |
| Lower Limit | | | 0.158 | 0.144 |
| Upper Limit | | | 169.961 | 155.545 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.045 | 0.041 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 93 | 85 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Pituitary: Chromophobe Adenoma[b] | 8/62 (13) | 0/5 (0) | 6/42 (14) | 5/46 (11) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.107 | 0.842 |
| Lower Limit | | | 0.339 | 0.230 |
| Upper Limit | | | 3.348 | 2.711 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.244 | 0.176 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 81 | 84 |
| Thyroid: C-cell Adenoma[b] | 2/65 (3) | 0/9 (0) | 3/39 (8) | 1/42 (2) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 2.500 | 0.774 |
| Lower Limit | | | 0.299 | 0.013 |
| Upper Limit | | | 28.669 | 14.321 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.156 | 0.013 |
| Upper Limit | | | Infinte | Infinite |
| Weeks to First Observed Tumor | -- | -- | 57 | 112 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Thyroid: C-cell Adenoma or Carcinoma[b] | 2/65 (3) | 0/9 (0) | 4/39 (10) | 1/42 (2) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 3.333 | 0.774 |
| Lower Limit | | | 0.499 | 0.013 |
| Upper Limit | | | 35.249 | 14.321 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.242 | 0.013 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 57 | 112 |
| Thyroid: Papillary Adenocarcinoma or Follicular-cell Adenoma[b] | 0/65 (0) | 0/9 (0) | 1/39 (3) | 2/42 (5) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.089 | 0.455 |
| Upper Limit | | | Infinite | Infinite |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.014 | 0.071 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | -- | 112 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Pancreatic Islets: Islet-cell Adenoma[b] | 3/72 (4) | 1/10 (10) | 0/42 (0) | 0/45 (0) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Departure from Linear Trend[e] | | P = 0.033 | | |
| Relative Risk (Pooled Control)[f] | | | 0.000 | 0.000 |
| Lower Limit | | | 0.000 | 0.000 |
| Upper Limit | | | 2.840 | 2.659 |
| Relative Risk (Matched Control)[f] | | | 0.000 | 0.000 |
| Lower Limit | | | 0.000 | 0.000 |
| Upper Limit | | | 4.444 | 4.155 |
| Weeks to First Observed Tumor | -- | 111 | -- | -- |
| All Sites: Hemangioma[b] | 0/75 (0) | 0/10 (0) | 0/48 (0) | 3/50 (6) |
| P Values[c,d] | P = 0.021 | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | -- | Infinite |
| Lower Limit | | | -- | 0.895 |
| Upper Limit | | | -- | Infinite |
| Relative Risk (Matched Control)[f] | | | -- | Infinite |
| Lower Limit | | | -- | 0.134 |
| Upper Limit | | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | -- | 99 |

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Photodieldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 5 or 10 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specific control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Photodieldrin in the Diet[a]

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Pituitary: Chromophobe Adenoma[b] | 12/62 (19) | 0/8 (0) | 4/48 (8) | 8/39 (21) |
| P Values[c,d] | N.S. | P = 0.038 | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.431 | 1.060 |
| Lower Limit | | | 0.107 | 0.409 |
| Upper Limit | | | 1.319 | 2.534 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.178 | 0.543 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 58 | 95 |
| Thyroid: C-cell Adenoma[b] | 1/66 (2) | 0/9 (0) | 2/43 (5) | 1/39 (3) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 3.070 | 1.692 |
| Lower Limit | | | 0.166 | 0.022 |
| Upper Limit | | | 176.825 | 129.471 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.069 | 0.014 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 106 | 112 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Thyroid: C-cell Adenoma or Carcinoma[b] | 2/66 (3) | 0/9 (0) | 2/43 (5) | 2/39 (5) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.535 | 1.692 |
| Lower Limit | | | 0.114 | 0.127 |
| Upper Limit | | | 20.387 | 22.398 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.069 | 0.077 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 106 | 112 |
| Thyroid: Papillary Adenoma, Papillary Adenocarcinoma, or Follicular-cell Adenoma[b] | 0/66 (0) | 0/9 (0) | 4/43 (9) | 0/39 (0) |
| P Values[c,d] | N.S. | N.S. | P = 0.022** | N.S. |
| Departure From Linear Trend[e] | P = 0.002 | | | |
| Relative Risk (Pooled Control)[f] | | | Infinite | -- |
| Lower Limit | | | 1.415 | -- |
| Upper Limit | | | Infinite | -- |
| Relative Risk (Matched Control)[f] | | | Infinite | -- |
| Lower Limit | | | 0.220 | -- |
| Upper Limit | | | Infinite | -- |
| Weeks to First Observed Tumor | -- | -- | 102 | -- |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Thyroid: Papillary Adenoma or Papillary Adenocarcinoma[b] | 0/66 (0) | 0/9 (0) | 3/43 (7) | 0/39 (0) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Departure From Linear Trend[e] | P = 0.007 | | | |
| Relative Risk (Pooled Control)[f] | | | Infinite | -- |
| Lower Limit | | | 0.920 | -- |
| Upper Limit | | | Infinite | -- |
| Relative Risk (Matched Control)[f] | | | Infinite | -- |
| Lower Limit | | | 0.142 | -- |
| Upper Limit | | | Infinite | -- |
| Weeks to First Observed Tumor | -- | -- | 102 | -- |
| Pancreatic Islets: Islet-cell Adenoma[b] | 1/69 (1) | 0/9 (0) | 0/49 (0) | 2/42 (5) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.000 | 3.286 |
| Lower Limit | | | 0.000 | 0.176 |
| Upper Limit | | | 26.256 | 189.114 |
| Relative Risk (Matched Control)[f] | | | -- | Infinite |
| Lower Limit | | | -- | 0.071 |
| Upper Limit | | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | -- | 100 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma, NOS[b] | 9/72 (13) | 0/9 (0) | 7/50 (14) | 10/49 (20) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.120 | 1.633 |
| Lower Limit | | | 0.376 | 0.642 |
| Upper Limit | | | 3.137 | 4.180 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.396 | 0.622 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 58 | 56 |
| Mammary Gland: Adenoma or Fibroadenoma[b] | 8/72 (11) | 0/9 (0) | 5/50 (10) | 10/49 (20) |
| P Values[c,d] | N.S. | P = 0.039 | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.900 | 1.837 |
| Lower Limit | | | 0.244 | 0.700 |
| Upper Limit | | | 2.920 | 4.945 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.256 | 0.622 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 81 | 56 |

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Uterus: Endometrial Stromal Polyp[b] | 7/67 (10) | 1/6 (17) | 5/42 (12) | 6/37 (16) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.139 | 1.552 |
| Lower Limit | | | 0.303 | 0.459 |
| Upper Limit | | | 3.868 | 4.940 |
| Relative Risk (Matched Control)[f] | | | 0.714 | 0.973 |
| Lower Limit | | | 0.116 | 0.171 |
| Upper Limit | | | 32.973 | 43.453 |
| Weeks to First Observed Tumor | -- | 111 | 81 | 112 |

[a]Treated groups received time-weighted average doses of 3.4 or 7.5 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specific control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS

IN MICE FED PHOTODIELDRIN IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Photodieldrin in the Diet[a]

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Lung: Alveolar/Bronchiolar Adenoma[b] | 5/77 (6) | 0/20 (0) | 1/47 (2) | 4/49 (8) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.328 | 1.257 |
| Lower Limit | | | 0.007 | 0.260 |
| Upper Limit | | | 2.792 | 5.529 |
| Relative Risk (Matched Control)[f] | | | Infinite | Infinite |
| Lower Limit | | | 0.023 | 0.393 |
| Upper Limit | | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | -- | 93 | 81 |
| Hematopoietic System: Lymphoma[b] | 0/78 (0) | 0/20 (0) | 1/47 (2) | 0/49 (0) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | Infinite | -- |
| Lower Limit | | | 0.088 | -- |
| Upper Limit | | | Infinite | -- |
| Relative Risk (Matched Control)[f] | | | Infinite | -- |
| Lower Limit | | | 0.023 | -- |
| Upper Limit | | | Infinite | -- |
| Weeks to First Observed Tumor | -- | -- | 93 | -- |

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 11/76 (14) | 3/18 (17) | 10/47 (21) | 9/47 (19) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.470 | 1.323 |
| Lower Limit | | | 0.603 | 0.520 |
| Upper Limit | | | 3.484 | 3.219 |
| Relative Risk (Matched Control)[f] | | | 1.277 | 1.149 |
| Lower Limit | | | 0.388 | 0.336 |
| Upper Limit | | | 6.657 | 6.094 |
| Weeks to First Observed Tumor | -- | 93 | 74 | 68 |
| Liver: Neoplastic Nodule or Hepatocellular Carcinoma[b] | 14/76 (18) | 3/18 (17) | 10/47 (21) | 10/47 (21) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 1.155 | 1.155 |
| Lower Limit | | | 0.497 | 0.497 |
| Upper Limit | | | 2.540 | 2.540 |
| Relative Risk (Matched Control)[f] | | | 1.277 | 1.277 |
| Lower Limit | | | 0.388 | 0.388 |
| Upper Limit | | | 6.657 | 6.657 |
| Weeks to First Observed Tumor | -- | 93 | 74 | 68 |

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Fed Photodieldrin in the Diet[a]

(continued)

[a]Treated groups received doses of 0.32 or 0.64 ppm in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specific control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Photodieldrin in the Diet[a]

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Lung: Alveolar/Bronchiolar Adenoma[b] | 2/78 (3) | 1/20 (5) | 0/48 (0) | 2/48 (4) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.000 | 1.625 |
| Lower Limit | | | 0.000 | 0.120 |
| Upper Limit | | | 5.493 | 21.678 |
| Relative Risk (Matched Control)[f] | | | 0.000 | 0.833 |
| Lower Limit | | | 0.000 | 0.047 |
| Upper Limit | | | 7.780 | 48.155 |
| Weeks to First Observed Tumor | -- | 93 | -- | 81 |
| Hematopoietic System: Lymphoma[b] | 3/79 (4) | 2/20 (10) | 1/49 (2) | 4/49 (8) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.537 | 2.150 |
| Lower Limit | | | 0.010 | 0.379 |
| Upper Limit | | | 6.442 | 14.050 |
| Relative Risk (Matched Control)[f] | | | 0.204 | 0.816 |
| Lower Limit | | | 0.004 | 0.130 |
| Upper Limit | | | 3.754 | 8.603 |
| Weeks to First Observed Tumor | -- | 92 | 93 | 88 |

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Fed Photodieldrin in the Diet[a]

(continued)

| Topography: Morphology | Pooled Control | Matched Control | Low Dose | High Dose |
|---|---|---|---|---|
| Liver: Hepatocellular Carcinoma[b] | 2/76 (3) | 0/19 (0) | 0/43 (0) | 1/47 (2) |
| P Values[c,d] | N.S. | N.S. | N.S. | N.S. |
| Relative Risk (Pooled Control)[f] | | | 0.000 | 0.809 |
| Lower Limit | | | 0.000 | 0.014 |
| Upper Limit | | | 5.958 | 15.027 |
| Relative Risk (Matched Control)[f] | | | -- | Infinite |
| Lower Limit | | | -- | 0.022 |
| Upper Limit | | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | -- | 93 |

[a]Treated groups received doses of 0.32 or 0.64 ppm in feed.

[b]Number of tumor-bearing animals/number of animals at site (percent).

[c]Beneath the incidence of tumors in a control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group (*) or with the pooled-control group (**) when $P < 0.05$ for either control group; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in a control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the specific control group.

# APPENDIX G

## ANALYSIS OF FORMULATED DIETS FOR CONCENTRATIONS OF PHOTODIELDRIN

APPENDIX G

Analysis of Formulated Diets for

Concentrations of Photodieldrin

A 10-g sample of the diet mixture was shaken with 125 ml benzene for 16 hours, then filtered through Celite with benzene washes. The combined extracts were reduced in volume and analyzed for photodieldrin by gas-liquid chromatography (electron capture detector, 10% DC-200 on Gas Chrom Q column). Recoveries were checked with spiked samples, and external standards were used for calibrations.

| Theoretical Concentrations in Diet (ppm) | No. of Samples | Sample Analytical Mean (ppm) | Coefficient of Variation (%) | Range (ppm) |
|---|---|---|---|---|
| 0.32 | 10 | 0.32(1) | 5.8% | 0.29-0.35 |
| 0.64 | 10 | 0.63(8) | 3.7% | 0.61-0.68 |
| 2.50 | 9 | 2.51 | 4.2% | 2.36-2.70 |
| 5.00 | 23 | 5.08 | 3.2% | 4.80-5.50 |
| 10.00 | 22 | 9.98 | 4.6% | 9.20-10.90 |

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